

The Myth of Sickle Cell Trait

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Recently emphasis in the problem of sickle hemoglobinopathy has been on mass screening of the black population. Concern about the alleged danger in having sickle cell trait itself is offered as part of the justification. This danger is disputed and a position developed for the benign status of sickle cell trait and the potentially serious social harm to blacks so identified. Programs are suggested to foster improved medical care availability and early detection for those with sickle cell anemia. It is suggested that mandatory patient programs be avoided, and that research receive greater emphasis.

SINCE EARLY 1971 screening blacks for the purpose of identifying persons possessing the gene for sickle hemoglobin has been a subject of great interest. Often, the impetus for this movement came from lay persons motivated by a genuine desire to serve the community. They were joined by many professional and governmental organizations equally well motivated. Lay publications, such as Reader's Digest,¹ speak of "identifying sickle cell carriers and thus preventing the disease through genetic counseling."

The clinics indicate counseling as their major program of remedy for the persons identified as having heterozygous or homozygous hemoglobin-S. The premise of prevention is advanced although the only way to prevent sickle cell anemia is for those who possess the hemoglobin-S gene either to avoid reproduction altogether or to predetermine the genetic pattern of any potential mate. It is contended that the person with sickle

cell trait is much sicker than was previously realized and therefore also needs guidance for this compromised state of health.

It is largely the hypothesis of a compromised state of health in the person with sickle cell trait that justifies the existence of programs of mass screening. This eventually resulted in the National Sickle Cell Anemia Control Act being passed by Congress in the spring of 1972. The act² clearly states that "efforts to prevent sickle cell anemia must be directed toward increased research . . . and the education, screening and counseling of carriers of the sickle cell trait." It allowed for up to twenty-five million dollars to be spent in 1973 on research and voluntary screening and counseling programs. This figure can be increased to fifty million in 1975. However, between 70 and 80 percent of funds are earmarked for mass screening and genetic counseling, with only 20 to 30 percent going to research and therapy. It is the purpose of this paper to examine the evidence relating to the heterozygous state of hemoglobin-S and to show that its negative effects on health have been exaggerated.

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Background

The homozygous-S state, henceforth to be called sickle cell anemia, is present when both hemoglobin genes are of the S variety. A single S gene, when combined with an A gene, constitutes what has been termed the A-S state, henceforth to be called sickle cell trait. In both the anemia state and the trait state, blood has the property of sickling when it has been subjected to sufficient deoxygenation (as in the so-called sickle cell preparation). Sickle cell trait can best be distinguished from sickle cell anemia or combinations of heterozygous-S with other non-A hemoglobin genes by electrophoretic techniques. The sickling phenomenon in this country is seen mainly in persons of African ancestry, but it has also been demonstrated in significant, although lesser, frequency among Sicilians, Arabs, some tribes of American Indians, and in some areas of Greece and Mexico. Screening programs that confine their efforts to blacks will therefore overlook a persistent reservoir of the gene.

It is well established that the incidence of sickle cell anemia among black Americans is approximately one in five hundred, and that between 7 and 10 percent of black Americans have the sickle cell trait. There are other heterozygous-S combinations which have definite pathologic importance but their combined incidence is much less than 1 percent of black Americans.³

The Ubiquitous Sickle Cell Trait

The sickle cell trait has been said to cause a variety of vascular thrombotic phenomena such as priapism, infarcts of pulmonary, splenic and cerebral vessels⁴ and the "sudden death syndrome."⁵

All of these are presumably mediated through dehydration, acidosis and anoxia, singly or in combination. Each of these clinical problems has had excellent documentation of association with sickle cell anemia. Since sickle cell trait has *in vitro* sickling in common with sickle cell anemia, it seemed logical to expect that enough dehydration, acidosis or anoxia in a person with trait ought also to produce *in vivo* sickling with similar clinical catastrophes. There is some support for that supposition in that autopsy examination of every cadaver with sickle cell trait does reveal the presence of intravascular sickling.^{6,7} However, this finding is due to the postmortem development of acidosis and anoxia that occurs regardless of

the initiating cause of death. This phenomenon may be part of the basis for the exaggeration of the consequences of sickle cell trait. There is reason to doubt that living man, with his homeostatic mechanisms functioning even poorly, is capable of reaching such desperate levels of imbalance as to lead to *in vivo* sickling in a person with sickle cell trait. This will be touched upon later.

Sickle cell trait does occasionally produce hyposthenuria and hematuria.⁸ Hyposthenuria creates no direct medical problems itself but is of academic interest. Hematuria appears in no more than 1 percent of people with sickle cell trait and although it rarely poses a life-threatening problem it can sometimes be a problem in differential diagnosis. Pregnancy in women with sickle cell trait has twice the likelihood of pyelonephritis that it has in pregnant women with normal hemoglobin,^{3,9} but there is no difference from normal persons in response to treatment. These two problems were mentioned first because they have excellent documentation in the form of large group case studies. Of great importance is the fact that there is no evidence relating their occurrence to altitude or other environmental hypoxia (such as swimming or anesthesia).

Priapism

Problems believed to be associated with sickle cell trait are often anecdotal, meaning they are reported in series so small that all conclusions are necessarily weakened. Priapism has had a well-documented association with sickle cell anemia, and the onset is usually in the pre-pubertal male. Recently an association with sickle cell trait has been claimed.¹⁰ Priapism has also long been known to occur idiopathically. Grace's series¹¹ had 11 idiopathic cases with an average age at onset of 40 years. Farrer's series¹² had 11 idiopathic cases with an average age at onset of 43 years. It is interesting that the three case reports¹⁰⁻¹² in which the condition is ascribed to sickle cell trait gave the age at onset as 34, 37 and 39 years—strikingly similar to the onset of the idiopathic variety.

Oral Contraceptives

In 1970 an article¹³ reported a case of a 20-year-old black woman with sickle cell trait who had a history of two years' use of oral contraceptives and a vertebro-basilar artery insufficiency syndrome. It was suggested the oral contraceptive

may have lowered oxygen tension sufficiently to have induced sickling. No evidence was offered as to how oral contraceptives could reduce oxygen tension in any direct manner. Nevertheless, this article has been the basis for the recently advanced proposal to withhold prescriptions of oral contraceptives from women with sickle cell trait.

Several population studies^{14,15} have shown the risk of thrombo-embolism in general is eight times greater among all women taking the pill, and the risk of cerebro-vascular disease in particular is six times greater than in women who are not taking the pill. For some unexplained reason young women who experience clinical stroke while taking oral contraceptives show at least a 25 percent incidence of involvement of the vertebro-basilar area of the brain.^{16,17} This area of the brain is involved only rarely in young persons with stroke who have not been taking oral contraceptives. This would seem to offer a different interpretation to the previously mentioned 1970 case report¹³ of the 20-year-old black woman who did indeed have a vertebro-basilar artery insufficiency syndrome.

General Anesthesia

General anesthesia for persons with sickle cell trait has been another matter of concern. The hypothesis is that such persons have a lowered tolerance of the anticipated hypoxia and possible acidosis associated with general anesthesia and the post-anesthetic state.^{18,19} There are some group studies available on the question. In 1969 a report from Kings County Hospital Center in New York²⁰ reviewed 47 sickle cell trait patients who had received 55 general anesthetics between 1956 and 1957. All patients had "smooth uncomplicated" hospital courses. In 1971 Oduntan and Isaacs²¹ reported experience with general anesthesia in 18 patients with sickle cell trait. There were no complications during anesthesia or in the post-operative period, although there were two later deaths. One occurred suddenly (presumably from a pulmonary embolus) 14 days after operation and the other, 15 days after operation, was caused by metastatic cancer found at operation. In neither instance was there evidence to link the combination of sickle cell trait and general anesthesia with the death two weeks later.

Sudden Death Syndrome

A connection with the "sudden death syndrome" was suggested by Jones, Binder, and

Donowho.⁵ They reported upon four black soldiers whose deaths they attributed to sickle cell trait. The deaths occurred during a 12-month interval at an Army basic combat training post which was situated at an altitude of 4,060 feet. During that time approximately 4,000 black soldiers underwent training in that facility. Four died suddenly, within 25 hours of becoming ill. All were black, had been exercising at this altitude, had the sickling phenomenon observed in their vasculature at postmortem and shared the mystery of having no other diagnosis. Of interest are several other points. One of the trainees lost consciousness while in the middle of running only once around his barracks and another soldier died within moments of his exercise which consisted simply of a 20-yard crawl. The 4,060-foot elevation of the Army post is not unduly high compared with many other points in this nation where black people live. The findings at postmortem of sickling throughout the vascular systems of the four soldiers has been explained earlier. The autopsy findings demonstrated no old infarcts that might have suggested previous sickling difficulties. Two of the recruits died of disseminated intravascular coagulation, yet there was no mention that any bacteriologic cultures had been obtained. A third recruit was found at postmortem to have "marked coronary arteriosclerosis." Previous studies by Kuller and others²² have shown that arteriosclerotic heart disease accounts for approximately 22 percent of all sudden, unexpected deaths in the 20-to-39-year age group, so that in this case there was an appropriate explanation without invoking sickle cell trait. The fourth recruit was anemic but hemoglobin electrophoresis had not been done, making it distinctly possible that he may have had a combination of hemoglobin-S with some other abnormal type of hemoglobin. These same objections have been pointed out by others.²³

A prospective study was done later on the same Army post by some of the original investigators.²⁴ Three months after the last of the four mysterious deaths, Binder and Jones identified 73 cases of sickle cell trait in the next 1,000 black recruits. These men were closely observed throughout their basic training (training that was identical to that given to the four men who had died "suddenly" during the preceding year). No morbidity and no deaths were observed. This article stressed that most persons with sickle cell trait were usually unaware of their abnormality.

Population Studies

There are epidemiologic approaches which can be used to determine if the mere possession of sickle cell trait itself is a threat to life. Three examples are as follows:

First, if a factor such as sickle cell trait is associated with a significant mortality, there should be an apparent difference in its frequency between those who die and those who continue to live over a given time span. In 1961 McCormick⁶ reported a survey for hemoglobin-S in the blood, at autopsy, of 1,248 black patients over the age of one month. These autopsies were performed during a 31-month period in three large hospitals in Tennessee. McCormick found sickle cell trait in 120 cases (9.6 percent). He also collected blood specimens from 1,660 living black patients in the same hospitals. The second group of specimens, from people who survived whatever had brought them to the hospital, served as controls against the autopsy group. In the group of 1,660 living patients, 140 (8.5 percent) had sickle cell trait. The difference between the two groups has no statistical significance.

Second, if sickle cell trait were contributing to death the average age at death of the affected persons should be lower than for those not affected. The 1,104 black patients in whom autopsy revealed normal (A-A) hemoglobin had an average age at death⁶ of 47.4 years. This is remarkable for its similarity to the average age at death in the sickle cell trait group (47.3 years).

Third and last, one can examine the incidence of a suspect condition in progressive age groupings. For example, if left-handedness were somehow a lethal handicap one should see progressively fewer left-handed people in older age groups. In 1970, Petrakis²⁵ and others looked for sickle cell trait in more than 4,000 black persons in an urban area in Northern California. The findings were grouped by ages of from 5 to 20, 21 to 49 and 50 years and over. The overall incidence of sickle cell trait was 8.7 percent and there was no statistically significant "change in frequency of sickle trait with advancing age."

High Altitude Flying

Much of the initial impetus for concluding sickle cell trait is dangerous came in some articles after World War II which sought to link sickle cell trait with splenic infarction during flight. In 1947 Sullivan²⁶ reported an 18-year-old

man in whom a probable splenic infarct developed while he was flying across the Rocky Mountains. Two months after subjective recovery the soldier's spleen was still palpable, though no longer tender. This soldier was also known to have significant target cell formation on peripheral blood smear. One would now consider this a likely case of either S-C or S-thalassemia disease rather than sickle cell trait as was originally concluded. Since electrophoresis was not available then, these possibilities could not have been explored.

During the next few years a number of observers reported²⁷⁻³⁰ isolated additional cases as they occurred. Hemoglobin electrophoresis and alkali-denaturation were added to the diagnostic armamentarium during that period. If the papers written by Conn,²⁷ Cooley et al,²⁸ Rotter et al,²⁹ and Smith and Conley³⁰ during the mid-1950's are read carefully, they compile the cases of 23 different persons with splenic infarction occurring during aerial flight. Twenty-one were examined by hemoglobin electrophoresis, and only four had alkali denaturation studies. Fourteen patients showed A-S hemoglobin patterns; eight of the 14 had either negative or highly questionable sickle cell preparations. This latter finding raises the distinct possibility that these persons with negative sickle cell preparations and "positive" electrophoretic patterns may have had hemoglobin-D trait rather than sickle cell trait. Hemoglobin-D and its properties (identical electrophoretic mobility with hemoglobin-S but no solubility change with deoxygenation)³¹ were not recognized at the time of those investigations and consequently could not have been considered. Of the 21 patients studied with electrophoresis, six had S-C disease, one had S-thalassemia and there is a very strong possibility that many of the remaining 14 either had S-thalassemia or combinations of hemoglobin-D trait.

A hematologic survey³ of 3,500 black women in a Washington, D.C., prenatal clinic indicated the A-S state was 16 times more frequent than A-D, which in turn was almost five times more frequent than S-C disease in that study group.

In 1945 an Air Corps study³² of black aviation cadets who were in various stages of training for both fighter and bomber groups was done at the Tuskegee Army Air Base. A group of black combat veteran pilots was also studied. The incidence of sickle cell trait was determined in each group and in the cadets who were eliminated from training. This study showed the incidence of sickle

cell trait at every stage of training (and in the combat veterans) stayed in the narrow range between 7.1 percent and 7.7 percent. The incidence of sickle cell trait among the cadets eliminated ranged between 4.4 percent in the primary trainees who "washed out" and zero in the more advanced trainees who failed. Such figures show the sickle cell trait trainees were at no discernible disadvantage.

More recent investigations³³ show that other hemoglobins have an interaction with hemoglobin-S when they are combined in a heterozygous molecule. This interaction influences the ability of a cell to sickle during deoxygenation. In ascending order of strength when combined with hemoglobin-S, hemoglobin A, C, and D are known to promote sickling during deoxygenation. Phrased another way, cells of hemoglobin A-S blood only begin to sickle at oxygen tensions of approximately 15 mm of mercury³⁴ while cells of hemoglobin S-C blood will begin to sickle at 30 mm of mercury. Cells with hemoglobin S-D will begin to sickle at oxygen tensions which approximate those noted for hemoglobin S-S (60 mm of mercury).³⁵

While arterial oxygen pressure at sea level is 100 mm of mercury, it slowly decreases with increasing altitude (for example, at 16,000 feet it is 40 mm of mercury). It becomes apparent why splenic infarctions associated with commercial air travel are not likely to be due to sickle cell trait.

The established incidence of the various combinations of other hemoglobins with S,³ the established importance of the interaction of these other hemoglobins on the ability of hemoglobin-S to sickle,³⁴ and the benign results of the Air Corps experience with sickle cell trait,³² suggests other possible explanations for the early case reports of splenic infarction due to high altitude flying. The very rarity of those cases suggests that what then seemed to be sickle cell trait (which is not rare) may have had a different explanation.

Genetic Counseling

If sickle cell trait is an essentially benign condition with no risk from hypoxia, the only justification for individual identification is that the bearer may participate in the production of offspring with sickle cell anemia. This is the heart of "genetic counseling" programs. It is proper to inquire into the validity of this approach.

Published data in the state of California³⁶ established that the total number of deaths from

all hemoglobinopathies (including sickle cell anemia) during the year 1969 was 20. The California Bureau of Vital Statistics has supplied unpublished information that in 1970 there were 26 such deaths. The 1970 national census showed 1.4 million blacks in California. This would mean an estimated 140,000 with sickle cell trait and 2,800 with sickle cell anemia.

Before screening 1.4 million people in search of genetic counseling subjects in order to prevent an illness which kills less than 26 of the parent group each year, the disadvantages must be weighed against the advantages. The mass screening approach does not consider fully the possible negative effects. Sickle cell screening was made mandatory in the District of Columbia as well as Virginia and Massachusetts. In Washington, D.C., there have been reported instances where sterilization has been recommended for children as young as the age of 12 simply because they had sickle cell trait.³⁷ Some parts of the insurance industry have already decided health and life insurance should be denied (or only issued with high-risk premiums) to people with sickle cell trait. Adverse effects on minority hiring have already been reported. A committee of the National Academy of Sciences and National Research Council has recommended that the United States Armed Forces screen all recruits and that those with sickle cell trait not be permitted to become pilots or co-pilots³⁸—this despite the available evidence which has previously been cited.

There has been no similar campaign to discourage diabetics from procreation although it could be similarly justified by geneticists. Most geneticists in sickle cell programs deny giving overt advice against having children, stating they only give information so the affected persons can make an "informed decision." This may be a euphemism for implied advice.

Recommendations

What is done should be as specific to the actual problem as possible. The immediate problem is the suffering of those afflicted with sickle cell anemia. Let us first insure that they have ready access to the best care currently available.

This can be done best by intensive education of the physicians of the country as to what is the best care. Educational programs for physicians could be sponsored and designed by state medical societies and medical schools. This

approach was used for the problem of leprosy in Hawaii, where, to be eligible to take the state licensure examination, every doctor must first complete a three- to four-hour course on leprosy given by the Health Department. Active leprosy in Hawaii has an incidence of only 6 per 100,000. Sickle cell anemia has an incidence of 14 per 100,000 in California. There are obvious differences between the two illnesses but the important point is the precedent of dealing with a unique medical problem in this unique fashion.

Second in immediacy is the problem of the still undiagnosed cases of sickle cell anemia. It would seem reasonable to have programs in which children between the ages of six months and six years would have at least one screening quantitative hemoglobin determination. Those that fall below an arbitrary point would be classed as having anemia, and then appropriate additional studies could be done to determine if the anemia was due to one of the hemoglobinopathies. If it was not, the information obtained from the screening quantitative hemoglobin determination would still be useful in taking affirmative helpful action for the patient. If sickle cell anemia or other hemoglobinopathy is found, the family and the attending physician are thus armed with important advance information that can spare the child later unnecessary discomfort. Such a program could be integrated into the programs of most well-baby clinics without undue difficulty.

Brief emphasis should be placed upon insuring that all such patient programs are voluntary. Mandatory programs for patients can easily be abused because the personnel engaged in them may lose sight of their original purpose. Voluntary programs tend to work because those participating know why they have elected to do so and see it through to its logical conclusions or leave the system when it no longer serves the client's need.

Of equal importance is the field of research. Additional research is needed into what produces a "crisis" at a given time. Additional avenues of therapy should be developed and explored.

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